

Appl. No. 10/007,331
Amdt. dated August 19, 2005
Reply to Office Action of April 21, 2005

PATENT

REMARKS/ARGUMENTS

Applicants acknowledge with appreciation the time taken by the Examiner during the interview on May 18, 2005. During the interview the rejections under 35 U.S.C. § 103 were discussed. Applicants appreciate the Examiner's helpful suggestions for addressing the outstanding rejections.

Status of Claims

After entry of this amendment, claims 57, 59, 61-65, 67-70, 101 and 113 are pending in the present application. Claim 57 has been amended to incorporate the limitations of claim 112, which is cancelled with this amendment. Support for new claim 113 is found for example at page 19, lines 7-12. No new matter is added with this amendment. Applicants specifically reserve the right to pursue the original claims in one or more subsequent applications.

In the Office Action mailed April 21, 2005, the Examiner reiterated the rejection of the claims for allegedly being obvious over Bergh *et al.* (US Patent 5,272,066), Maras *et al.* (USP 5,834,251), Weinstein *et al.* (*J. Biol. Chem.*, 257:13845) and Williams *et al.* (*Glyconconjugate J.* 12:255). Claims 57, 59-65, 67-70, 101 and 112 are rejected under the doctrine of obviousness-type double patenting over claims in the parent patent (US Patent 6,399,363). Each of these rejections will be addressed in the order in which they were raised.

Rejection under §103(a)

The rejection of the claims over the cited prior art is respectfully traversed. Briefly, the Examiner cites Bergh *et al.* and Maras *et al.* for teaching *in vitro* methods of enzymatic modification of glycoproteins using sialyltransferases, including ST3Gal III. The Examiner acknowledges, however, that neither reference teaches a commercial-scale method, nor does either reference discuss the extent of sialylation achieved in the methods. The Examiner cites Weinstein *et al.* for allegedly teaching conditions under which sialyltransferases can fully sialylate a substrate. Williams *et al.* is cited for allegedly teaching large scale recombinant expression of sialyltransferases.

Appl. No. 10/007,331
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To establish a *prima facie* case of obviousness, the Examiner must meet three basic criteria. First, the Examiner must show that there is some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, the Examiner must show a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991) and MPEP § 2142. To support the rejection, the examiner must "present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985) and MPEP § 2142.

As explained in the specification, a commercially feasible means for producing sufficient amounts of sialyltransferases is preferred for commercial-scale methods for *in vitro* sialylation (see e.g., page 8, line 30 to page 9, line 11). According to the specification at page 18, line 30 to page 19, line, yields of enzymes purified from natural sources are typically not feasible for commercial-scale methods. In the present response, applicants have amended claim 57 to specify that the sialyltransferases used in the methods of the invention are recombinantly produced.

In the Office Action, the Examiner states that one of skill would expect that 80% sialylation could be achieved in commercial-scale methods, based on the cited prior art. In particular, on page 5, the Examiner asserts that the teachings of Williams *et al.* would lead one of skill to expect that the high levels of sialylation shown by Weinstein *et al.* could be achieved in a large scale method using recombinantly produced enzymes. The Examiner cites nothing in Williams to show that 80% sialylation was achieved using the enzymes described there. Indeed, Williams *et al.*, actually provides evidence as to why one of skill would *lack* a reasonable expectation that recombinantly produced sialyltransferases would retain appropriate kinetic properties to render them practical in a commercial scale synthetic method. As the title suggests, Williams *et al.* compared the kinetic properties of recombinant sialyltransferases to those of

Appl. No. 10/007,331
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PATENT

corresponding native enzymes. As shown in Tables 1 and 2 and discussed on page 759 in the paragraph bridging the left and right columns, the recombinant proteins generally had lower affinity (higher K_m) for substrate (CMP-NeuAc, oligosaccharide or glycoprotein), as compared to the native enzymes. Moreover, the authors found that the specific activity of the recombinantly produced $\alpha 2,3$ sialyltransferase had a specific activity about 1/3 of that of the native enzyme (*see* page 760, bottom of left column). The authors speculate in the Discussion Section on page 759, that differences in glycosylation in the recombinantly produced enzymes may account for the alterations in the kinetic properties.

Applicants respectfully submit that a proper showing of why one of skill would expect high levels of sialylation using recombinant sialyltransferases, in light of the teachings of Williams *et al.*, has not been provided. In the absence of such a showing the rejection is improper and should be withdrawn.

With this amendment, applicants have also added claim 113, which is directed to recombinant expression of sialyltransferases in *Aspergillus niger*. The specification provides evidence that this expression system is surprisingly efficient. At page 19, lines 5-15, different recombinant expression methods are discussed. There it is explained that for *A. niger* expression, yields are about 1000 U/liter, whereas yeast expression has been reported at 0.3 U/liter. Thus, *A. niger* expression levels are over 3,000 times those achieved in yeast. *A. niger* expression levels are also 40 times those described by Williams *et al.*, who report yields of about 25 U/liter (*see* Williams *et al.*, page 756 second column).

In conclusion, the pending claims require that the commercial scale methods of the invention achieve sialylation levels of at least 80% **and** that the enzyme be recombinantly produced. The prior art provides no evidence that a commercial-scale method, using a recombinantly produced enzyme, can achieve 80% sialylation levels as claimed here. To support the rejection, the Examiner simply asserts that one of skill could scale up prior art methods without addressing the teaching in the cited references. To maintain the present rejection, however, the Examiner must provide a convincing line of reasoning as to why the artisan would use recombinant enzymes in the methods of the invention, in light of the evidence that the kinetic

Appl. No. 10/007,331
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PATENT

properties of recombinant enzymes are not the same as native enzymes. In the absence of such a showing, applicants respectfully submit the rejection is improper and should be withdrawn.

In addition, recombinant expression of sialytransferases in *A. niger*, is not suggested by the art of record. Moreover, the yields from this expression system are surprisingly high compared to other recombinant expression systems known at the time of the invention. In light of this evidence applicants respectfully submit that new claim 113 is patentable over the prior art.

In previous responses, applicants have provided extensive evidence of the commercial success of the present invention. In particular, applicants have shown that over 20 successful feasibility studies have been carried out (*see* Zopf Declarations 1 and 2). Applicants have also provided evidence of a number of commercial licenses based on successful feasibility studies. Nonetheless, at page 7 of the Office Action, the Examiner questions whether evidence of use agreements and feasibility studies is sufficient to establish commercial success.

Applicants respectfully submit that such studies are indeed evidence of the commercial success of the claimed methods. Since use agreements are negotiated at arms length with sophisticated third parties, entering into such agreements is, itself, evidence of commercial success. Moreover, the evidence of record clearly shows that pharmacokinetics and other therapeutic properties of recombinant proteins can be improved using the methods of the invention.

With regard to the nexus between the claimed invention and commercial success, the Examiner suggests that the lower concentration of enzyme used in the preferred embodiments of the invention (and which is not explicitly recited in the claims), may account for the commercial success of the claimed methods. In particular, on pages 9 and 11 of the Office Action, the Examiner appears to suggest that cost savings resulting from lower enzyme levels may be relevant to the success of the claimed invention. Although the present inventors found that surprisingly low levels of enzyme are required to achieve high levels of sialylation, the commercial success is due to the improved pharmacokinetic and therapeutic results, not the lowered costs. As noted in Exhibit 1 to the Second Zopf Declaration, sales of recombinant

Appl. No. 10/007,331
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PATENT

therapeutic proteins can be extremely high. For example, annual sales of erythropoietin reaches \$5 billion worldwide. The cost savings achieved by using low levels of enzyme in the claimed methods is not significant compared to worldwide sales of most therapeutic proteins. Thus, the cost savings resulting from lower enzyme concentration is not related to the commercial success of the claimed invention.

Applicants respectfully submit that advertising and promotional activities are not relevant in the relevant marketplace where the consumer is free to choose on the basis of objective principles. The collaborations described above are the result of arms length negotiation between sophisticated parties. Thus, applicants respectfully submit that the Zopf Declarations and Appendices 1-6 establish a nexus between the claimed invention and evidence of commercial success.

As such, the foregoing secondary indicia represents objective evidence sufficient to rebut a *prima facie* case of obviousness. Accordingly, the Examiner is respectfully requested to withdraw the 35 U.S.C. §103(a) rejection and send this application to issue.

Obviousness-type Double Patent Rejection

In response to the obviousness-type double patenting rejection over claims in the parent patent (US Patent 6,399,363), Applicants will file an appropriate terminal disclaimer, once the outstanding rejection under §103(a) is resolved.

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CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at 415-576-0200.

Respectfully submitted,


Kevin Bastian
Reg. No. 34,774

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 415-576-0200
Fax: 415-576-0300
Attachments
KLB:klb
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